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Rehan M. Khan, Chung-Hay Luk, Adeen Flinker, Amit Aggarwal,
Hadas Lapid, Rafi Haddad, and Noam Sobel

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14. ABSTRACT

Although it is agreed that physicochemical features of molecules determine their perceived odor, the rules governing this relationship
remain unknown. A significant obstacle to such understanding is the high dimensionality of features describing both percepts and
molecules.Weapplied a statistical method to reduce dimensionality in both odor percepts and physicochemical

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Predicting Odor Pleasantness from Odorant Structure: Pleasantness as a Reflection of the Physical World

Rehan M Khan, Chung-Hay Luk, Adeen Flinker, Amit Aggarwal, Hadas Lapid, Rafi Haddad, and Noam Sobel

Foreword

The mapping of various physical stimulus attributes onto perception is well defined in vision and audition, but not in olfaction. Other than the mapping of molecular concentration onto perceived odor intensity (Cain, 1969), there is no known general systematic mapping of molecular properties onto the olfactory percept. In other words, there is no scientist or perfumer who can predict the smell of a novel molecule by its physico-chemical structure, or the physico-chemical structure of a novel smell.

Understanding this link between physico-chemical structure and percept has been elusive because the percept is in large part plastic, dependent on experience and learning (Brennan and Keverne, 1997; Wilson and Stevenson, 2006). Nevertheless, part of the olfactory percept is innate and hard wired. For example, laboratory rodents that have never encountered a cat through generations of breeding still react fearfully to cat-odor, but not other novel and noxious odors (Dielenberg and McGregor, 2001). Yet the link between physico-chemical structure and this hard-wired portion of the percept has proven equally elusive.

This may be due in part to the complexity of both the perceptual space and the stimulus space. The perceptual space is made of *odors*, that can be described by a large number of verbal descriptors. The stimulus space is made of *odorants*, relatively small molecules (Ohloff, 1986), that can be described by a large number of physico-chemical descriptors. Verbal descriptors for a large number of odorants have been reliably obtained, revealing considerable agreement in several aspects of olfactory perception (Dravnieks, 1982, 1985), and physico-chemical descriptors can be mined and computed (Tetko et al., 2005) from structures available in chemical data-bases (e.g., PubChem). Thus, we sought to

construct a perceptual space from verbal descriptors, an analogous physico-chemical space from chemical descriptors, and then test for any systematic relation between these two spaces.

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Statement of the problem studied

Although it is agreed that physico-chemical features of molecules determine their perceived odor, the rules governing this relationship remain unknown. A significant obstacle to such understanding is the high dimensionality of features describing both percepts and molecules. We applied a statistical method to reduce dimensionality in both odor percepts and physico-chemical descriptors for a large set of molecules. We found that the primary axis of perception was odor pleasantness, and critically, that the primary axis of physico-chemical properties reflected the primary axis of olfactory perception. This allowed us to predict the pleasantness of novel molecules by their physico-chemical properties alone. Olfactory perception is strongly shaped by experience and learning. However, our findings suggest that olfactory pleasantness is also partially innate, corresponding to a natural axis of maximal discriminability amongst biologically relevant molecules.

Summary of the most important results

Materials and Methods

Subjects

One hundred and eighty five subjects (96 F) between the ages of 19 and 39 participated in the experiments after providing informed consent to procedures approved by the UC Berkeley Committee for the Protection of Human Subjects. Subjects were generally healthy, with no history of neurological disease, nasal passage disease, broken nose or septoplasty.

Location and stimuli

Experiments 1-6 were conducted in stainless-steel-coated rooms designed to minimize olfactory contamination. Experiment 7 was conducted in a well ventilated concrete room in the Arab village of Dir El Asad in the Northern Galilee part of Israel. All odorants were from Aldrich Chemicals, of the highest purity available, and matched for perceived intensity by dilution with mineral oil or deionized distilled water as appropriate. The odorants used are detailed in Supplementary Tables 5 and 6, and referenced in the results section per experiment. Intensity-matching dilution procedures used a group of 10 experienced subjects used only for that purpose. Intensity matching was obtained by first identifying those odorants that were perceived as least intense in their undiluted form by 2 experimenters. Diluted samples were prepared for each more intense odor by the 2 experimenters and judged to be of the same intensity as the least intense odors. These prepared odors were then presented to each of the 10 rating subjects, who rated their

intensity using a visual-analog scale (VAS). Pairwise differences between odors were tested using paired t-tests. For any odor pair showing a significant difference in intensity, the more intense odor was diluted and was re-rated by the group of 10 rating subjects until no significant differences in perceived intensities were evident.

Perceptual estimation studies

Perceptual estimates were obtained by rating the applicability of the property of interest onto a given odorant using a visual-analog scale (VAS). All interactions with subjects during experiments were by computer, with an experimenter viewing behavior from a neighboring room via video monitor and one-way window. Odorants were sniffed from jars marked arbitrarily (e.g., Jar A001). Experimental instructions were provided by computer using digitized voice, and perceptual estimates were obtained through mouse clicks on a visual-analog scale (VAS) 20 cm long. For example, in an experiment on odorant pleasantness, in a given trial the subject would hear a digitized voice reading: "*Please sniff jar A001 at the tone, three, two, one, TONE*", then the subject would hear: "*Please rate odorant pleasantness*". At this time a 20 cm long VAS line would appear on the monitor, with the labels "extremely pleasant" at one end of the line, and "extremely unpleasant" at the other. Subjects would initiate a mouse-click at a point along the line that reflected their perception. For the different experiments, scale extremes were "low similarity" vs. "high similarity", "extremely pleasant" vs. "extremely unpleasant", “edible (foods)” vs. “inedible (toxic items)”, "Not at all flowery" vs. "Extremely flowery" and "Not at all sweet" vs. "Extremely sweet". In every experiment subjects also rated intensity ("very low intensity" vs. "extremely high intensity"), and in any case where,

despite the initial intensity-matching procedure, an odorant was an outlier in terms of perceived intensity (>2STD), it was deleted from further analysis (this occurred for only 4 odorants out of the 90 odorants tested across experiments). VAS values (in mm) were Z-scored for every subject across odorants. All inter-stimulus-intervals ranged from 30 to 45 seconds. Odorant presentation order was counter-balanced across subjects.

Reaction time study

We used a 40 trial forced choice same-different discrimination task (4 second inter-sniff interval) using 5 odorants. Stimuli were presented using an olfactometer that delivered odorants into a nasal mask with ~2 ms temporal resolution (Johnson et al., 2003; Johnson and Sobel, 2007). On every trial, subject heard a digitized voice instructing to sniff at the tone, followed by a second sniff instruction 4 seconds later. Subjects then had to respond within 2.5 seconds by pressing one of two buttons that denoted either "same" or "different". The response interval ended with a buzzer if no response was recorded. The ITI was set to 45s so as to minimize adaptation. Each odorant was presented 8 times, 4 times paired with itself, and once paired with each of the other 4 odorants. After pooling all the same-same pairs as one condition ("same"), this matrix generated 11 possible pairings.

PCA analysis for dimension reduction

To reduce the dimensionality of perceptual descriptors previously obtained by Dravnieks (Dravnieks, 1982, 1985), and of physico-chemical descriptors obtained using Dragon software (Talete srl, Milano, Italy), we used the principal component function in the

Statistics Toolbox of MATLAB (The Mathworks Inc., Natick MA, USA). In brief, PCA takes a data set consisting of N points in an M-dimensional space (for example, 160 odorants in the 146-dimensional odor descriptor space in the case of the Dravnieks data) and finds a rotation matrix which rotates the N points onto a new M-dimensional space with certain special properties. These are 1) that the new dimensions are orthogonal and 2) that the new dimensions, called principal components, e.g. PC[1], PC[2], …, PC[M], are ordered so that each successive PC has the maximal possible variance. Thus PC[1] explains the most variance of any linear transform of the original data space, PC[2] explains the next biggest amount of variance, and so on. Because the PCs are orthogonal, they explain mutually exclusive sets of variance. The entire set of M PCs thus accounts for all the variance in the original data set. In practice, for data spaces in which the apparent dimensionality exceeds the intrinsic dimensionality (as is the case, for example, when many of the dimensions are intercorrelated or redundant) relatively few PCs will capture most of the variance in the original data space. A notable difference between PCA and other methods of multivariate analysis such as "factor analysis" is that in PCA the does not depend upon the user to specify a particular data model, or to make a priori decisions regarding which data is to be included or excluded.

Because Dragon generated a very large number of physico-chemical descriptors (1513, Supplementary table 4, available at http://www.weizmann.ac.il/neurobiology/worg/materials.html), we did not apply PCA to only the 144 Dravnieks odorants, but rather to 1565 odorants commonly used in olfactory experiments and the fragrance industry (Supplementary Table 8). This assured that all principal components could be estimated, and robustly. Each descriptor was normalized

by z-scoring to prevent descriptors with larger ranges from artefactually dominating the dimensionality of the descriptor space.

After PCA, one can generate a subspace onto which one can project the data. For example, figure 1b contains the 144 monomolecular odorants from Dravnieks projected onto a subspace made of the first 4 PCs (although only two are shown in the two-dimensional graph). In other words, each odorant is now described by 4 numbers rather than the original 146. Distances between odors using these 4 numbers were calculated using a Euclidean distance metric, i.e.

$$D = \mathrm{sqrt}(\sum (x_i - y_i)^2)$$

where **x** and **y** are the vectors for 2 different odors and i ranges over 1,2,..4.

Building a model from physico-chemical onto perceptual olfactory space

We modeled each perceptual PC independently as a linear combination of the physico-chemical PCs plus an error term:

$$\mathbf{Y}_i = \mathbf{X}\mathbf{b}^t + \mathbf{e}_i$$

where $\mathbf{Y}_i$ is the vector of the i^{th} perceptual descriptor (or i^{th} PC of the perceptual space), **X** is a matrix of the predictive physico-chemical descriptors and **b** is the weighting on **X** to fit **Y** and $\mathbf{e}_i$ is Gaussian noise. Fitting was done by least squares.

We used a step-wise cross-validation procedure to determine inclusion of physico-chemical PCs. We increased the number of physico-chemical PCs to predict perceptual PC1 until an increase resulted in no increase in predictive power. Predictive power of each model was tested as follows: we randomly divided the set of 144 odorants into 2 sets of 72, a model-building set and a test set. A model was built using the current number of physico-chemical PCs and then this model was applied to the 72 odorants in the test set. The correlation between the predicted and actual values in the test set measures the power of the model. This cross-validation procedure was repeated1000 times for each size of model, and a distribution of each predictive measure was obtained. This procedure resulted in a model including the first 7 physico-chemical PCs.

Results

Constructing a perception-based space

We constructed a perceptual odor space using data from Dravnieks' *Atlas of Odor Character Profiles*, wherein ~150 experts (perfumers and olfactory scientists) ranked (from 0 to 5, reflecting "absent" to "extremely" representative) 160 odorants (144 monomolecular species, and 16 mixtures) against each of the 146 verbal descriptors (Dravnieks, 1985) (the lists of odorants and descriptors are in Tables 1 and 2 of the supplementary materials).

We applied principal components analysis (PCA), a well-established method for dimension reduction, that generates a new set of dimensions (principal components or PCs) for the profile space in which: 1) each successive dimension has the maximal possible variance and 2) all dimensions are uncorrelated. Figure 1A shows the

percentage of the variance in the perceptual feature space explained by each of the first 10 PCs. As can be seen, the effective dimensionality of the odor profile space was much smaller than 146, with the first 2 PCs accounting for 40.1% of the total variance in the odor profiles, and the first 4 accounting for 54%. The full weighting of all 146 descriptors on the first four PCs is listed in Table 1 of the supplementary materials.

By selecting a number of PCs we can define a perceptual space. Figure 1b contains a 2-dimensional projection of the odorants onto the subspace formed by the first and second PCs. In such a space, similar odorants are understood to be close to one another and dissimilar odorants are understood to be distant from one another (a navigable version of this space is available at http://www.weizmann.ac.il/neurobiology/worg/odorspace/Ptplot5.5/ptolemy/plot/demo/FourierSeries.htm).

Validating the perception-based space

To test our perceptual feature space, in Experiment 1 we obtained pairwise perceived similarity ratings from 21 subjects for each of 9 odorants that were pseudo-randomly selected to span the space of the first 4 PCs (detailed in Fig 1b). Pairwise similarities for each of the 36 possible odorant pairs were compared to pairwise Euclidean distances in our perceptual PC space using the first 1, 2, 3, 4, and 5 PCs. The addition of each successive component increased the correlation with the explicit pairwise similarity ratings until the 5^{th}, which showed no statistically significant improvement in the correlation. Figure 1c shows the near linear relationship between the Euclidean distance over the first 4 PCs and the average pairwise similarity of our raters ($r = -0.71$

$F(1,34)=34.37$, $p<0.0001$). Pairwise similarity values for the odors can be found in Supplementary Table 3.

In Experiment 2 we tested our perceptual space using an implicit similarity task. Using 5 of the 9 previously used odorants (detailed in Fig 1b), we presented 21 subjects with a forced choice speeded reaction time task in which subjects were presented with 2 odorants in succession and required to indicate as quickly as possible whether they were the same or different. As expected (Wise and Cain, 2000; Abraham et al., 2004; Rinberg et al., 2006), subjects took longer to make correct judgments for more similar odorant pairs than for dissimilar odorant pairs (Figure 1d), where similarity was derived from our 4 dimensional perceptual space ($F(1,9)=36.48$, $r = .80$, $p<0.0002$). Thus, in both explicit and implicit similarity tasks our derived perceptual space corresponded to subjects' judgments of similarity.

Identifying the primary dimension of the perception-based space: Pleasantness

The descriptors that flank the first PC of perceptual space ranged from "sweet" and "floral" at one end, to "sickening" and "rancid" at the other (Figure 2a, and Table 1 in supplementary materials), suggesting that the first PC of perceptual space may be pleasantness (referring to the continuum from unpleasant to pleasant, also referred to as *perceptual valence* or *hedonic tone*).

To test this, in Experiment 3, 10 subjects rated the pleasantness and intensity of the 9 odorants used in Experiment 1. To compare these results with the PCA results, for each pair of odorants we computed a pleasantness distance (the absolute difference between their ratings) and regressed this against their distance based on the first PC.

Whereas these two measures were strongly correlated (see Figure 2b, $F(1,34) = 55.1$, $r= 0.79$, $p<0.0001$), a similar analysis on the intensity estimates revealed no significant correlation ($F(1,34) = .46$, $r= -0.12$, $p > .5$).

As an second test of whether perceptual PC1 reflects odor pleasantness, we compared previously published pleasantness ratings for each of the 146 perceptual descriptors used (Dravnieks et al., 1984) (note, these are pleasantness ratings associated with the descriptors, not the odorants), to the component weights on the first PC. Figure 2c shows the component weights, sorted by value for the first PC. Figure 2d shows the previously collected pleasantness ratings plotted against component weights. The relationship between rated pleasantness and component weights was clearly not linear, so in order to assess the relationship we first transformed the component weights with a sigmoid transform, which we then regressed against the pleasantness ratings. The correspondence between descriptor pleasantness and the first PC weighting was quite strong ($r=0.74$, $F(1,144)=$, $p<0.0001$).

As a third test, we asked whether the term “pleasantness” is better at capturing the first PC of perception when compared to individual related descriptors such as "sweetness" or 'floweriness", both of which had the among the highest weight on perceptual PC1 (see Figure 2a). In Experiment 4, 22 subjects rated the "pleasantness", "floweriness", and "sweetness" of 22 odorants randomly selected from the 144 odorants used by Dravnieks. As predicted, ratings of all three labels were significantly correlated with PC1 values (Pleasantness, $r = 0.83$, $p<0.0001$; Sweetness $r = 0.73$, $p<0.0016$; Floralness, $r = 0.63$, $p<0.0138$), but the correlation of PC1 with "pleasantness" was significantly higher than the correlations for "sweetness" and "floweriness" (binomial

sign test on difference in r scores across subjects: Pleasantness vs. Sweetness, $p < 0.0262$; Pleasantness vs. Floralness, $p < 0.0001$; Sweetness vs. Floralness, $p < 0.0022$), suggesting that this label captures significantly more of the variance in PC1 than do even closely related terms (see Figure 2e).

Experiments 3 and 4, combined with several additional analyses detailed in the supplementary materials, and an additional test of "edibility" as an alternative label to perceptual PC1 (to be described later in the results), all supported our observation that the first PC reflected odor pleasantness.

Building a Physico-chemical Molecular Descriptor Space

To relate this perceptual space to physico-chemical properties of molecules, we used a similar procedure to reduce the dimensionality of the physico-chemical space. We obtained 1514 physico-chemical descriptors for each of 1565 odorants. These descriptors were of many types, e.g., atom counts, functional group counts, counts of types of bonds, molecular weights, topological descriptors and so on. Applying PCA revealed that the effective dimensionality of the space of descriptors was much lower than the apparent dimensionality of 1514. Figure 3a shows the percent variance explained by each of the first 10 PCs. The first PC accounted for ~32% of the variance, and the first 10 accounted for ~70% of the variance. Figure 3b shows the 5 descriptors that anchor the first PC of the space (the full names of these physico-chemical descriptors are listed in the legend of Figure 3 and in Supplementary Table 4, that also lists the full weighting of all 1513 descriptors on the first five PCs, available at http://www.weizmann.ac.il/neurobiology/worg/materials.html).

Identifying the primary dimension of physico-chemical space

Characterizing the primary dimension of the PCA space of the physico-chemical descriptors is more complex than the task for the perceptual space, both because of the set-size and the variety of descriptors involved. The first physico-chemical PC was weighted at one end by factors which are reasonable proxies for molecular size or weight: the sum of the atomic van der Waals volumes is essentially a crude count of atoms, as is the count of the number of non-hydrogen atoms, and the self-returning walk count of order one for non-hydrogen atoms (which is actually identical to a count of the non-hydrogen atoms). The characterization of these descriptors as indices of "weight" is borne out by the very high weighting that "molecular weight" itself has on this side of the first PC: -0.044 (Supplementary Table 4, available at http://www.weizmann.ac.il/neurobiology/worg/materials.html).

At the other end of the dimension, are a series of topological descriptors that vary with the "extent" of a molecule. In fact, all 5 of the descriptors are average eigenvectors of distance or adjacency matrices, normalized in slightly different ways: average eigenvector coefficient sum from electronegativity weighted distance matrix, average eigenvector coefficient sum from Z weighted distance matrix (Barysz matrix), average eigenvector coefficient sum from mass weighted distance matrix, average eigenvector coefficient sum from distance matrix, average eigenvector coefficient sum from adjacency matrix. Each of these measures increases as the denseness of the atomic connections increases, i.e. as the number of atoms is packed more closely together. In combination then, these two extremes anchor a dimension which characterizes the

amount and distribution of mass within a molecule. That said, unlike the case of the perceptual data where we also applied an intuitively simple label to PC1 (pleasantness), we have no equally valid label for PC1 of physico-chemical organization, and characterization of the true nature of this dimension awaits detailed analysis of all the relevant physico-chemical features involved in its construction. Supplementary Figure 4 shows some representative molecules arranged in the space of the first and second physico-chemical PCs.

Building a Model from Physical to Perceptual Space

We have used PCA to construct two spaces: a perceptual space and a physico-chemical space. PCA generates ordered sets of orthogonal axes, constructed to maximize the variance they capture in the original feature space. Because the axes are uncorrelated (orthogonal) we can compare them independently.

For each of the four perceptual PCs we asked whether they were correlated with any of the first few physico-chemical PCs. Each of the 4 panels in Figure 4A corresponds to one of the first 4 perceptual PCs. Each panel shows the correlation of a single perceptual PC with the first 7 physico-chemical PCs. Error bars represent 1 std error of the mean derived from 1000 bootstrap replicates. Strikingly, the strongest correlation was between the first perceptual PC and the first physico-chemical PC (for 1000 bootstrap replicates, this correlation ($r = .49$, $p < 0.001$) was significantly stronger than correlations between the 1^{st} physico-chemical PC and the 2^{nd} ($r = .11$, $p < .001$), 3^{rd} ($r = .12$, $p < .001$), and 4^{th} ($r = .20$, $p < .001$) PCs of perception. This correlation was also significantly stronger than the correlation between the 1^{st} perceptual PC and the 2^{nd}

physico-chemical PC ($r = .11$, $p < .001$)). In other words, there was a privileged relationship between PC1 of perception and PC1 of physico-chemical organization. The single best axis for explaining the variance in the physico-chemical data was the best predictor of the single best axis for explaining the variance in the perceptual data. The higher order, and lower variance dimensions of the perceptual space were more correlated with higher order, and lower variance physico-chemical dimensions.

Having established that the physico-chemical space is related to the perceptual space, we next built linear predictive models through a cross-validation procedure. Figure 4B shows the correlation between the first perceptual PC and its predicted values resulting from the model based on the first 7 physico-chemical components ($r = 0.59$, ($F(1,136)=10.62$, $p<0.0001$). In other words, we generated a model that predicted odor perception from odorant structure.

Experimental Validation: Predicting the Perceptual Qualities of Novel Molecules

To test the predictive power of our model, we obtained physico-chemical parameters for 52 odorants commonly used in olfaction experiments, but not present in the set of 144 used in the foregoing experiments and model building (Table 5 in the Supplementary Materials). We applied our model to the 52 new molecules so that for each we had predicted values for the 1^{st} PC of perceptual space. The distribution of predicted 1^{st} PC values is shown in Figure 5a.

As an initial test, in Experiment 5 we pseudo-randomly selected a subset of 5 of the 52 odorants which spanned the range of 1^{st} PC values and asked 14 subjects to rank these 5 odorants (equated for intensity) in order of pleasantness-unpleasantness. The

median ranking for each of the 5 odorants sorted by expected ranking from our model is shown in Figure 5b. As can be seen, subjects' rankings of the 5 odorants matched the predicted ordering from our model (Spearman Rank correlation $r = 0.72$, $p<0.0004$).

In Experiment 6 we selected 27 of the 52 molecules at random and asked 20 subjects to rate the pleasantness-unpleasantness of each. Figure 5c shows a plot of the predicted first PC value against the average pleasantness rating. The two measures were significantly correlated ($r = 0.55$, $F(1,25)=10.64$, $p < 0.004$). These results confirm those of the cross-validation procedure: a model based upon physico-chemical properties of molecules can provide a good prediction of the perceived pleasantness-unpleasantness of those molecules.

Cross-Cultural Validation

Judgments of pleasantness and other olfactory properties can vary across cultures (Wysocki et al., 1991; Ayabe-Kanamura et al., 1998; Hudson, 1999). Given that molecules are universal but that olfactory perceptions may be culturally specific, in Experiment 7, we tested our predictive model in 3 different cultures: among Americans in California, Muslim-Arab Israelis, and Jewish Israelis. To test our model, we selected 27 new odorants (not in the Dravnieks set and not tested in the previous prediction experiments) that were 1) odorous and 2) were used very infrequently in human olfaction experiments (details in supplementary Table 7) so as to minimize any bias towards commonly used odors. Finally, we addressed the possibility that an alternative characterization of the first PC might be "edibility" or food-like vs. nonfood-like odors.

In addition to rating pleasantness, subjects from all three cultures also rated edibility of odorants for which we predicted PC1 values.

Figure 6a-c shows plots of the mean ratings of pleasantness and Figure 6d-f show mean ratings of edibility from each of the 3 cultural groups plotted against predicted PC 1 values from our physico-chemical model. In all cases the model predictions were better correlated with the pleasantness than the edibility judgments (Americans: Pleasantness $r = 0.53$, $F(1,25) = 9.99$, $p < 0.004$, Edibility $r = 0.27$, $F(1,25) = 1.9$, $p > 0.05$; Muslim Arab-Israelis: Pleasantness $r = 0.57$, $F(1,25) = 12.14$, $p < 0.002$, Edibility $r = 0.38$, $F(1,25) = 4.32$, $p < 0.048$; Jewish-Israelis: Pleasantness $r = 0.49$ $F(1,21) = 6.65$, $p < 0.018$, Edibility $r = 0.26$, $F(1,21) = 1.47$, $p > 0.05$) indicating that our predictions were valid across cultures, and that perceptual PC 1 better reflects pleasantness than edibility. In addition, judgments of pleasantness were more consistent across cultures than judgments of edibility: Americans and Arab-Israeli judgments of pleasantness were correlated $r = 0.70$ ($F(1,25) = 24.17$, $p < 0.0001$) whereas judgments of edibility were correlated $r = 0.46$ ($F(1,25) = 6.70$, $p < 0.02$). Similarly, Americans and Jewish-Israeli judgments of pleasantness were correlated $r = 0.71$ ($F(1,21) = 21.24$, $p < 0.0002$). The correlation in judgments of edibility was higher than that between Americans and Arab-Israelis ($r = 0.69$ ($F(1,21) = 19.41$, $p < 0.0002$) possibly reflecting the more European eating habits of Jewish Israelis compared to Arab Israelis.

Discussion

We first reduced the dimensionality of olfactory perception, and observed that pleasantness is the principal perceptual aspect of olfaction. This characterization of the

first PC as pleasantness is in agreement with previous research (Richardson and Zucco, 1989). Pleasantness is the primary perceptual aspect humans use to discriminate odorants (Schiffman, 1974; Godinot and Sicard, 1995), or combine them into groups (Berglund et al., 1973; Schiffman et al., 1977). Pleasant and unpleasant odorants are evaluated at different speeds (Bensafi et al., 2002), and by dissociable neural substrates, as evidenced in both electrophysiological recordings (Kobal et al., 1992; Pause and Krauel, 2000; Masago et al., 2001) and functional neuroimaging studies (Zald and Pardo, 1997; Royet et al., 2000; Gottfried et al., 2002; Anderson et al., 2003; Rolls et al., 2003). Finally, studies with newborns suggest that at least some aspects of olfactory pleasantness may be innate (Steiner, 1979; Soussignan et al., 1997). Thus, our initial finding here is consistent with the view that "it is clearly the hedonic meaning of odor that dominates odor perception" (Engen, 1982).

We next reduced the dimensionality of physico-chemical properties, and identified a primary axis of physico-chemical space. This axis was weighted at on end by measures reflecting molecular weight, and at the other end by measures reflecting molecular extent. Although it is temting to label such a continuam, for the main finding of this manuscript, the importance lies in identifying a first PC of physico-chemical space (i.e., an ordering of 1513 molecular descriptors), and not in its label.

The key finding of this manuscript was that 144 molecules were similarly ordered by these two independently obtained principal axes, one for perception and one for physico-chemical structure. In other words, when physico-chemical measures with no *a priori* connection to any particular percepts were analyzed, those physico-chemical measures that were best at discriminating a set of molecules were found to be those that

were most correlated with the perception of olfactory pleasantness. In other words, when one orders a set of odorants based on the variance in their physico-chemical properties alone, they end up roughly ordered by perceptual pleasantness as well. This phenomenon allowed us to predict ($r = \sim.5$, $p < \sim.004$) odorant pleasantness of more than 50 molecules that we didn't smell before (and that were not part of our model building set), that were here tested in more than 80 subjects spanning three cultures. This ability to predict perceptual properties of novel odorants was a critical aspect of this manuscript. One may argue that the odorants selected by Dravnieks were somehow skewed, or that our choice of method for dimension-reduction (PCA) has limitations, or that our model building was somehow erroneous. Such concerns would gain increased weight if all we did was predict within the test set, that is, from one portion of the modeled data onto another portion of the modeled data (as in Figure 4B). However, considering that we made predictions on novel odorants outside of the test set (Figure 5B, 5C, 6A, 6C, 6E) suggests that we have revealed a genuine mechanism that is independent of the odorants used to build the model, or the particular methods of dimension reduction and model-building that we applied.

A main consequence of these results is that they provide a perceptually validated and physico-chemically constrained metric for probing the olfactory system. For example, this result suggests a framework for selecting candidate ligands to test for affinity to particular olfactory receptors, and for axes of spatial encoding in olfactory bulb and cortex. One can simply select odorants from the olfactory perceptual space (a navigable version of this space is available at http://www.weizmann.ac.il/neurobiology/worg/odorspace/Ptplot5.5/ptolemy/plot/demo/F

ourierSeries.htm), and test the hypothesis that extent of distance within the space reflects extent of difference in neural response, whether amplitude, rate, or location.

All that said, it is important to stress the limitations of our claim. First, one qualifier to our predictive abilities is that they relate to odorants that have been equated for perceived intensity. Intensity and pleasantness interact in complex ways (Henion, 1971; Doty, 1975; Moskowitz et al., 1976), and our model requires additional refinement to reflect this complexity. Furthermore, as in other senses, the perception of odor, and of pleasantness, is a complex process involving both innately tuned and learned components. We do not suggest that there is a rigid transform from odorant structure to odor perception that will ultimately explain all of perception. Olfactory perception and subsequent neural representations are significantly influenced by several aspects clearly unrelated to physico-chemical structure, such as context (Schoenbaum and Eichenbaum, 1995; Kay and Laurent, 1999; Herz and von Clef, 2001), expectation (de Araujo et al., 2005; Zelano et al., 2005), multisensory convergence (Haberly, 2001; Gottfried and Dolan, 2003; Rolls, 2004) and various top-down state-dependent modulatory influences (Pager, 1983; Critchley and Rolls, 1996; Kay and Freeman, 1998; Murakami et al., 2005). Furthermore, olfactory perception is a heavily learned process (Brennan and Keverne, 1997; Wilson and Stevenson, 2006), that critically depends on past and ongoing experience and exposure (Keverne, 1995; Wilson, 2003; Davis, 2004). The dynamics of this dominant aspect of olfactory perception will obviously not be reflected in physico-chemical structure. However, a portion of olfactory perception is innate and hard-wired (Dielenberg and McGregor, 2001), and our results concern this part.

A final important caveat about our results is the relatively simple nature of our predictive model. We were able to predict the pleasantness of new odors using a simple linear model on physico-chemical descriptors. While a linear model is a useful simplification of a complex problem, and was able to account for ~30% of the variance in the data, it is unlikely that real olfactory systems will be linear. No doubt, more complex, nonlinear models of the mapping from physico-chemical to perceptual space, which will require much larger datasets to develop and independently test, will have significantly more explanatory power.

That perceptual pleasantness is a reflection of optimal physico-chemical discrimination may at first appear at odds with the notion that olfactory pleasantness is both variable across individuals and cultures (Wysocki et al., 1991; Ayabe-Kanamura et al., 1998), and also malleable within individuals over time (Cain and Johnson, 1978; Hudson, 1999; Stevenson and Repacholi, 2003). Thus, given our result, how does one explain existing variance in perceived pleasantness? Even when the pleasantness scale reflects an organizational aspect of the physical world, an initial rigid encoding of odor pleasantness may be recoded at later stages of processing to reflect changing contingencies obtained through experience and learning (Brennan and Keverne, 1997; Wilson and Stevenson, 2006). Indeed, the olfactory system is known for plasticity at multiple levels (Graziadei et al., 1979; Wilson et al., 2004; Barkai, 2005; Mandairon et al., 2006), that reflects an advantageous evolutionary mechanism. To automatically reject food that smells fermented is generally a safe bet. However, if through experience one learns that exceptions exist, and for example fermented fish can be both tasty and healthy, than its pleasantness representation may shift. This is what allows Swedes to

enjoy their Surströmming Herring (a dish not for the faint of heart), although even they won't say they like the odor *per se*. Finally in this respect, it is notable that although our predictive power for pleasantness was significant ($p < .004$), we explained only a portion of the variance. This leaves open the possibility that individual differences and plasticity in olfactory hedonics make important contributions to olfactory perception.

In this study we probed the link between physico-chemical properties and odor perception. Past studies have approached this by varying stimuli along a single and simple physico-chemical dimension such as carbon chain length (Laska and Teubner, 1999), or a single and simple perceptual descriptor (Rossiter, 1996) such as "bitter almond like" (Zakarya et al., 1993). Here, rather than moving from chemistry to perception, we went from perception to chemistry, and probed a large set of physico-chemical descriptors using an unbiased statistical approach. In this, we have followed in the footsteps of Schiffman, Amoore, Dravnieks, and others, that together laid the groundwork for this approach between the early 1950s to late 1970s (Amoore, 1963; Laffort and Dravnieks, 1973; Schiffman, 1974). In this respect, the contribution of the current work is in observing that the perception of pleasantness corresponded to a physico-chemical axis that was the best single discriminator of molecules that have a smell. This enabled a critical component of this manuscript, namely, predicting perceptual aspects of a novel odorants that were not in the original test set.

In conclusion, we generated an olfactory perceptual space, and a molecular physicochemical space. Relating these spaces to each other allowed us to predict a moderate portion of the variance in olfactory perception, but more critically, led us to conclude that the major axis of perception reflects the major axis of physico-chemical

organization. Whereas the particular labels applied to the primary axes of perception and physico-chemical organization may be modified through future research, or interpreted differently by different researchers, we suggest that the privileged link between PC1 of perception and PC1 of physico-chemical organization reflects an organizational property of the sense of smell.

Figure Legends

Figure 1. Olfactory perceptual space. A: The proportion of variance in perceptual descriptions explained by each of the PCs (starting at ~0.3), and the cumulative variance explained (starting at ~0.05). B: The 144 odorants projected into a 2-dimentional space made of the first and second PCs. The 9 odorants used in Experiment 1(acetophenone, amyl acetate, diphenyl oxide, ethyl butyrate, eugenol, guaiacol, heptanal, hexanoic acid, and phenyl ethanol) are in enlarged cirles, and the 5 odorants used in Experiment 2 (acetophenone, amyl acetate, ethyl butyrate, eugenol, guaiacol) are in further enlarged circles. C: For the 9 odorants, the correlation between explicit perceived similarity ratings and PCA-based distance for all pairwise comparisons. Odorants closer in the perceptual space were perceived as more similar. D: Reaction time for correct trials in a forced-choice same-different task using 5 of the 9 odorants. Error bars reflect SE. Reaction time was longer for odorant-pairs that were closer in PCA-based space, thus providing an implicit validation of the perceptual space.

Figure 2. Identifying pleasantness as the first PC of perception. A. The 5 descriptors that flanked each end of PC1 of perception. We should stress that here, and in Figure 3B, we show the 5 extreme descriptors only to help give a sense of the PC. This does not reflect a cutoff in any stage of the analysis, but only an esthetic cutoff for the figure. B. For the 9 odorants, the correlation between the pairwise difference in pleasantness and the pairwise distance along the first PC. Distance along the first PC was a strong predictor of difference in pleasantness . C: The 146 perceptual descriptors plotted as a

function of their weighting on the first PC of perception. D: The previously published pleasantness associated with each one of the 146 perceptual descriptors. The descriptors clearly weighted on the first PC of perception in accordance with their pleasantness . E: We randomly selected 21 odorants previously tested by Dravnieks (Acetyl Pyridine, Benzaldehyde, Amyl Acetate, Camphor dl, Celeriax, Citral, Dimethyl Pyrrole2,5, Eugenol, Heptanal, Hexanoic acid, Hexanol1, Hexanol3, Indole, Methyl-iso-Borneol2, Methyl Quinolinepara, Octanol1, Octenol-1-3-OL, Phenyl Ethanol, Skatole, Vanillin) and had 22 subjects rate all odorants using 3 scales with VAS extremes of "Not at all flowery" vs. "Extremely flowery", "Not at all sweet" vs. "Extremely sweet", and "extremely unpleasant" vs. "extremely pleasant". Order of VAS scales was counter balanced. Judgments were converted to z-scores for each subject, and scores for odorants averaged across subjects. We then regressed these normalized ratings against the PC1 values for these odorants.

Figure 3. Reducing dimensionality of physico-chemical space. A: The proportion of variance in physico-chemical descriptors explained by each of the PCs (starting at ~0.32), and the cumulative variance explained (starting at ~0.01). B: The 5 descriptors that weighted most heavily at the ends of PC1 of physico-chemical space. The descriptors are: sV = 'sum of atomic van der Waals volumes (scaled on Carbon atom)'; Xu = 'Xu index'; Xov = 'pleasantness connectivity index chi-0'; nSK = 'number of non-H atoms'; SRW01 = 'self-returning walk count of order 01 (number of non-H atoms, nSK)'; VEe2 = 'average eigenvector coefficient sum from electronegativity weighted distance matrix';

VEZ2 = 'average eigenvector coefficient sum from Z weighted distance matrix (Barysz matrix)'; Vem2 = 'average eigenvector coefficient sum from mass weighted distance matrix'; VEA2 = 'average eigenvector coefficient sum from adjacency matrix'; VED2 = 'average eigenvector coefficient sum from distance matrix.

Figure 4. Relating physico-chemical space to perceptual space. A: The correlation between the 1st to 4th (descending in the figure) perceptual PC and each of the first 7 physico-chemical PCs for the 144 odorants. Error bars reflect SE from 1000 bootstrap replicates. The best correlation was between the first PC of perception and the first PC of physico-chemical space. This correlation was significantly larger than all other correlations. B: For the 144 odorants, the correlation between their actual first perceptual PC value and the value our model predicted from their physico-chemical data.

Figure 5. Predicting perception of novel odorants.. A: The distribution of predicted first PC values for 52 novel odorants. B: The median pleasantness ranking for each of 5 odorants that spanned the first predicted PC, sorted by expected ranking from our model. C: The correlation between the rated pleasantness of 27 out of the 52 odorants and the first PC value as predicted by our model.

Figure 6. A-C: Cross-cultural validation. Twenty-seven odorous molecules not commonly used in olfactory studies, and not previously tested by us were presented to 3 cultural groups of naïve subjects: Americans (23 subjects), Arab-Israelis (22 subjects) and Jewish-Israelis (20 subjects). In all cases, our predictions of odorant pleasantness

were in fact better than in the test data (Figure 4B). D-F. Ratings of edibility for the same odorants and groups. Across all cultures, our predicted PC1 values were significantly better correlated with judgments of pleasantness than judgments of edibility.

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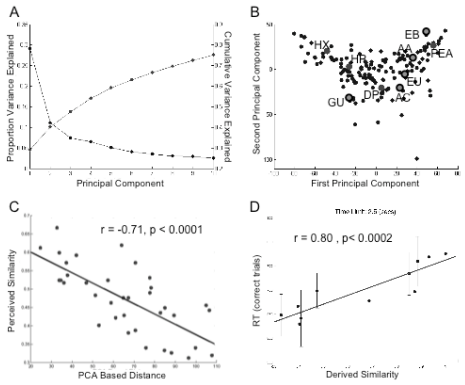
Appendixes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First Principal Component
HX
EB
AA
EA
EU
GU
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AK
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D
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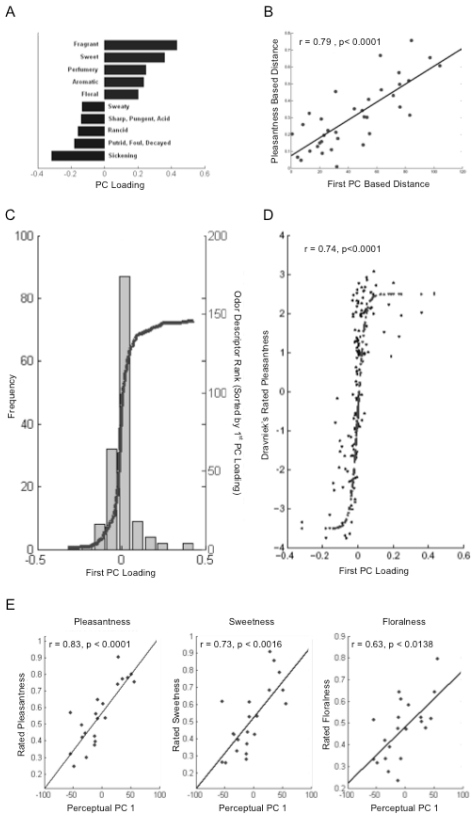
RT (correct trials)
Derived Similarity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Floral
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Sharp, Pungent, Acid
Rancid
Putrid, Foul, Decayed
Sickening
PC Loading
B
r = 0.79 , p< 0.0001
Pleasantness Based Distance
First PC Based Distance
C
Frequency
Odor descriptor Ranks (Scored by 1st PC Loading)
First PC Loading
D
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Dravnieks Rated Pleasantness
First PC Loading
E
Pleasantness
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Rated Pleasantness
Perceptual PC 1
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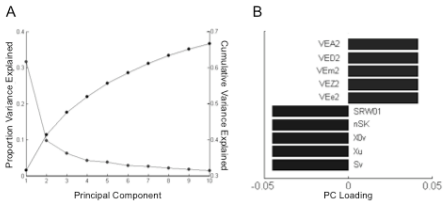
Rated Floralness
Perceptual PC 1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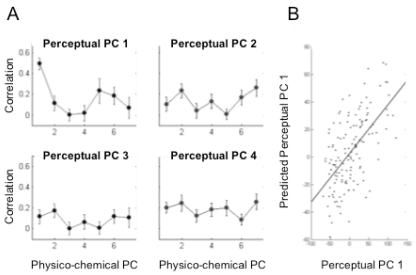
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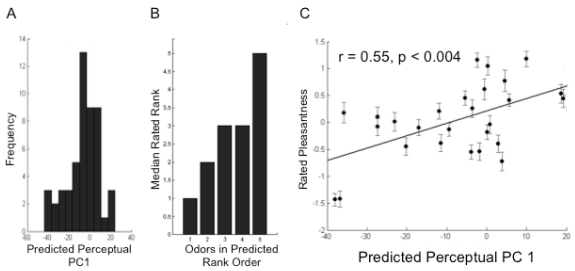
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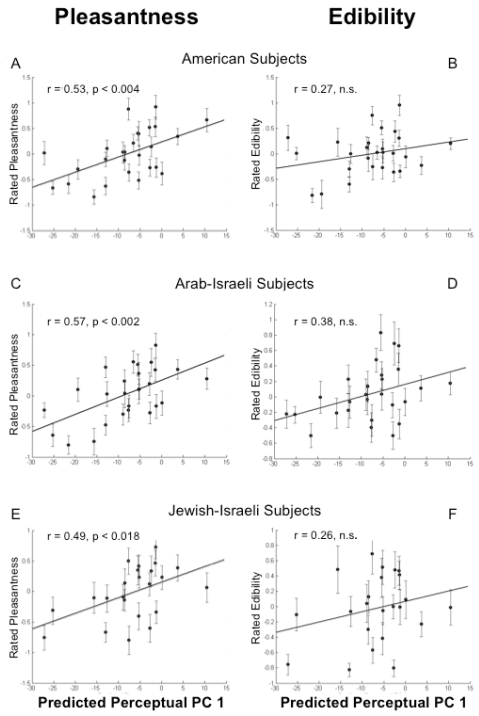
Pleasantness
Edibility
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Rated Edibility
C
Arab-Israeli Subjects
D
r = 0.57, p < 0.002
r = 0.38, n.s.
Rated Pleasantness
Rated Edibility
E
Jewish-Israeli Subjects
F
r = 0.49, p < 0.018
r = 0.26, n.s.
Rated Pleasantness
Rated Edibility
Predicted Perceptual PC 1
Predicted Perceptual PC 1